REMARKS

Claims 1, 10, and 14-17 were pending at the time of the Office action. Claims 1, 10, and 15-17 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 1, 10, and 15-17 stand rejected under 35 U.S.C. § 103(a). Applicants address each of these matters below.

Claim Amendments

Claims 10 and 17 have been canceled. Claim 1 has been amended to feature individuals "exhibiting low bone mass or decreased bone mineral density." Support for this amendment is found, for example, on page 1, lines 4-8 of the specification as filed, which states that the invention relates to antagonists of placental growth factor and "the use of such antagonists to prevent bone loss or bone mass and to enhance bone healing including the treatment of conditions which present with low bone mass and/or bone defects in vertebrates, and particularly mammals, including humans" (emphasis added). Additional support for this amendment is found, for example, on page 2, lines 18-20 of the specification as filed, which states that "[a]n object of the present invention is to provide a medicament for the treatment of osteoporosis in higher mammals exhibiting decreased cortical bone mineral density and preventing osteoporosis due to cortical bone mineral density reduction in such mammals" (emphasis added).

Claim 1 has also been amended to recite antibodies and functional fragments thereof. Support for this amendment is found, for example, on page 3, lines 14-20 of the specification as filed, which states that the invention is directed to "anti-PlGF antibodies and functional fragments derived thereof, anti-sense RNA and DNA molecules and ribozymes that function to inhibit the translation of PlGF, all capable of interfering/or inhibiting the VEGFR-1 signal transduction" (emphasis added).

New claims 19-22 are directed to subject matter of canceled claims 10 and 17. These claims feature antagonists of PlGF, including anti-sense nucleic acids against placental growth factor, interference RNA against placental growth factor, and ribozymes against placental growth factor. Claims 20 and 22 are directed to methods for reducing bone resorption by employing tetrameric peptides that bind specifically to placental growth factor.

The present amendments were made solely to expedite prosecution, and Applicants reserve the right to pursue any canceled subject matter in this or a continuing application. No new matter has been added.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 10, and 15-17 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner states (page 4) that "[t]he term 'antagonist of placental growth factor' encompasses a large genus." Specifically, the Examiner has

interpreted "small molecules binding on P1GF or VEGFR-1," "peptides or tetrameric peptides binding on PlGF," and "antibodies binding on PlGF," presented in canceled claim 10, as encompassing a broad range of compounds.

Applicants note that claims 10 and 17 have been canceled and that new claims 19-22 are no longer directed to small molecules or peptides. Accordingly, Applicants submit that the claims, as amended, refer to a limited number of antagonists of PlGF, examples of which were known to one skilled in the art prior to the filing date of the present application. More particularly, tetrameric peptide antagonists interacting specifically with PlGF are disclosed in Example 10 of WO 01/85796 (Carmeliet et al.), which is incorporated by reference into the current application (see, e.g., page 9, line 23 of the specification as filed). Antisense nucleic acids against placental growth factor are described in Yonekura et al. (*J. Biol. Chem.* 274:35172-8, herein "Yonekura;" copy enclosed). Yonekura demonstrates that the administration of antisense nucleic acids against the PlGF gene was capable of reducing the level of PlGF-1 and PlGF-2 in endothelial cells (page 35176, left column, first paragraph), thereby showing that antisense nucleotides are effective PlGF antagonists. Applicants submit that other oligonucleotide-based antagonists, such as interference RNA and ribozymes, behave similarly to antisense RNA to inhibit the activity of P1GF (see, e.g., page 3, lines 31-34). The specification extensively describes other nucleic acid based antagonists, such as those found on page 10, line 29 to page 16, line 20.

As such, Applicants submit that, in this case, it would not require undue experimentation to employ antagonists of PlGF as claimed.

Claims 1, 10, and 15-17 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states (page 6) that "[t]here is insufficient descriptive support for the genus 'antagonist of placental growth factor,' 'peptides binding on PlGF,' 'antibodies binding on PlGF,' 'tetrameric peptides binding on PlGF or VEGFR-1,' and 'small molecules binding on placental growth factor or VEGFR-1.'" Applicants submit that there is no doubt that the specification "allows the person of ordinary skill in the art to recognize what is claimed," as required based on *Vas-Cath Inc. v. Mahurkar* 19 U.S.P.Q.2d 1111, cited by the Examiner (page 7). Indeed, there can be no question that one of ordinary skill would readily recognize PlGF antagonists, as encompassed by the present set of claims.

All of the antagonists used for practicing the claimed methods were either available in the art or could be produced by standard techniques at the time of filing, based on the known nucleic acid (e.g., antisense, interference RNA, and ribozymes) or protein sequence (e.g., antibodies and tetrameric peptides) of placental growth factor. Moreover, in view of their structure-function relationship to the placental growth factor nucleic acid or protein sequence, PlGF antagonists were readily recognized as such by the skilled person. As all of the claimed antagonists exert their effect in the same way (i.e., reduce functional PlGF levels leading to a reduction of bone resorption, as illustrated in

representative model systems in the Examples section), Applicants submit that the inventors were plainly in possession of the claimed invention at the time of filing.

Applicants submit that the enablement and written description requirements with respect to antagonists of placental growth factor are amply met in the specification as filed. Accordingly, the rejection under 35 U.S.C. § 112 should be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 10, and 15-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Murakami et al. (JP 2001086982 A), in view of Robinson et al. (*FASEB* 15:1215-7, 2001) and Dias et al. (*PNAS* 98:10857-62, 2001). The Examiner states (page 10) that it is "obvious for a skilled person to use the teaching of Murakami et al. to inhibit the action of VEGFR-1 on osteoclasts to include VEGFR-1 antagonists such as anti-VEGFR-1 antibodies or small molecules binding VEGFR-1." Without acquiescence to the objection, the claims have been amended to remove reference to antagonists binding to VEGFR-1. The Examiner has not presented any arguments indicating that the use of antagonists directed to PlGF or the PlGF gene are described in the cited prior art documents. Accordingly, Applicants submit that the rejection under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 7/13/2007

James D. DeCamp
Reg. No. 43,580

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045